Mycobacterium chimaera infections associated with heater–cooler units in cardiac surgery

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Abstract: Purpose of review: Mycobacterium chimaera infections following cardiac surgery have been reported from an increasing number of countries. These infections are characterized by a poor prognosis with a case fatality rate around 50% despite treatment. Since the first description in 2013, our understanding has grown steadily. Several outbreak investigations, case series, and experiments with heater–cooler units (HCUs) have been published. This review summarizes the current knowledge. Recent findings: M. chimaera transmission occurs during cardiopulmonary bypass via bioaerosols emitted from contaminated HCU water systems. Manifestations of M. chimaera infection comprise endocarditis, vascular graft infections, surgical site infections, and dissemination. So far, all cases were exposed to a single HCU brand. Samples from the manufacturing site as well as clonality of M. chimaera strains isolated from HCUs and patients suggest a contamination already at time of delivery representing the main source for the outbreak. Nevertheless, HCU contamination in hospitals cannot be excluded. Summary: Improved awareness of physicians of M. chimaera infection is crucial to prompt adequate diagnostic workup in patients that have been exposed to HCU presenting with compatible symptoms. For risk mitigation, strict separation between the air volume in contact with HCUs and critical clinical areas such as operating rooms is essential.

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Summary
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Keywords
heater–cooler device, heater–cooler unit, *mycobacterium chimaera*, nontuberculous mycobacteria

INTRODUCTION

Following an initial report on the outbreak investigation of *Mycobacterium chimaera* infections after open heart surgery, a steadily increasing number of cases has been reported from several countries [1–5]. This review addresses the current knowledge of this global *M. chimaera* outbreak (Table 1).

M. chimaera, one of the latest members of the *Mycobacterium avium* complex, was first described in 2004 [6]. Clinical reports identified *M. chimaera* as a relatively rare cause of mycobacterial lung disease [7]. Pulmonary infections caused by *M. chimaera* are considered equally or less virulent than *Mycobacterium intracellulare* [7,8]. More recently, *M. chimaera* contamination has been identified in a number of water-containing medical devices such as heater–cooler units (HCUs) of various brands [9▪▪,10,11▪,12▪▪], extracorporeal membrane oxygenators [13], hyper–hypothermia systems feeding cooling–warming blankets (personal communication P.W.S. and H.S.), and water fountains [9▪▪].

Owing to the association with *M. chimaera* infections, HCUs have come into the focus of infection prevention and control teams, public health and regulatory authorities, and the public. HCUs are a functional part, yet standalone device, of the extracorporeal circuit in surgery requiring cardiopulmonary bypass and responsible for temperature regulation of blood and cardioplegia solution. Water is used as heat transfer medium because of its ideal properties for this purpose. Superfluous heat is typically dissipated by a radiator and a fan.

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KEY POINTS

- Contamination of LivaNova 3T HCUs with *M. chimaera* likely occurred during production, but contamination of any HCU at the local level remains relevant.
- Airborne transmission of aerosolized *M. chimaera* from HCU water to affected individuals during cardiac surgery.
- *M. chimaera* infections are characterized by latency up to 5.1 years, poor prognosis: curability remains uncertain.
- HCU-associated *M. chimaera* infections are likely underdiagnosed.
- Sustainable decontamination of contaminated HCUs has not yet been established, necessitating strict separation of HCU from operating room air.

TRANSMISSION OF *MYCOBACTERIUM CHIMAERA* DURING CARDIAC SURGERY

Historically, blood-borne infections originating from the heart–lung machine were reported [14], but in modern devices such leaks are very rare [15]. *M. chimaera* aerosolize from contaminated HCUs and settle on surgical instruments, the open wound, or directly on implant surfaces. Invasive *M. chimaera* infections have always occurred in association with foreign materials such as prosthetic valves, grafts, and wires [16▪,17▪▪]. Following local biofilm formation and replication, the bacteria disseminate to bone marrow, liver, lungs, urinary tract, and retina [17▪▪,18,19,20▪]. However, recently several studies report detecting *M. chimaera* in the water system of LivaNova 3T (London, UK; formerly Sorin, Germany; formerly Stöckert) HCUs. *M. chimaera* could also be detected in air samples or sedimentation plates positioned in a room with running, but not with nonrunning HCUs that were contaminated [9▪▪,10,21▪▪]. Matching random amplified polymorphic DNA PCR patterns between water and corresponding air samples confirmed *M. chimaera* aerosolization further [9▪▪]. The hydrophobic nature of cell membrane of mycobacteria results in exceedingly high concentration of *M. chimaera* at water surfaces and consequently, in bioaerosols [22]. A feature of LivaNova 3T HCUs is the presence of several fans, a large one for heat dissipation in the lower part and smaller fans in the upper part of the device to cool electronic components. One study located aerosolization leakage and dissipation by an upper fan [10]. Aerosol release has been traced to leakage at the edge of the tank's roof [12▪▪]. Experiments using particle counters and smoke showed that airflow and emitted bioaerosols of LivaNova HCUs can disrupt the ultraclean air system designed to protect the operating field [21▪▪].

Similar experiments with other HCU brands are missing. Two experiments produced negative results for the alternative hypothesis of direct transmission via water-to-blood leakage through a defective oxygenator membrane. Intraoperative blood cultures of 32 patients with surgery using contaminated HCUs did not produce *M. chimaera* [9▪▪]. A surrogate blood circuit on prolonged extracorporeal circulation with a *M. chimaera* contaminated HCU remained without mycobacterial growth [10].

ORIGIN OF HEATER–COOLER UNIT CONTAMINATION

Nontuberculous mycobacteria are known to colonize hospital water systems [23] and contaminate medical devices. Hence, HCU contamination at the hospital level cannot be excluded and other nontuberculous mycobacteria besides *M. chimaera* might pose a similar risk. Recently, contamination from tap water with *Mycobacterium abscessus* resulting in HCU-associated infections was reported [24▪▪].

Increasing evidence points toward a clonal strain of *M. chimaera* related to one manufacturer's device being responsible for the majority of cases in the current international outbreak. Already in the first case report about two surgery-related *M. chimaera* infections; a match between patient isolates by random amplified polymorphic DNA PCR was reported [25]. Current studies employed whole genome sequencing to compare *M. chimaera* patient strains and found them to be almost identical. A recent study described clonality among isolates from HCUs and patients in Denmark and the USA [26▪]. In a cluster of 11 patients and samples derived from five LivaNova 3T HCUs, a genetic distance of maximal 38 single nucleotide polymorphisms across a core genome of circa five million base pairs was seen [27]. Similarly, clonal *M. chimaera* isolates were described in HCU water samples and one cardiac surgery patient from Australia and New Zealand, also matching the 11 US patient strains [5].

Until now, all cardiac surgery-associated cases were associated with LivaNova 3T HCUs. One has to consider, however, that devices of other manufacturers are much less prevalent [28]. Water samples from the water pump assembly area at the LivaNova production site as well as from factory-new HCUs confirmed the presence of *M. chimaera* pointing to a contamination at the time of production [16▪]. In August 2014, *M. chimaera* positive environmental samples at the manufacturing site prompted

Table 1. Accumulating evidence on the *Mycobacterium chimaera* outbreak in cardiac surgery

Publication	Origin	Contribution to understanding the problem
Achermann *et al.* [25]	Zurich, Switzerland	Report on first two patients with identical strains by random amplified polymorphic DNA PCR.
Sax *et al.* [9▪▪]	Zurich, Switzerland	Discovery of infectious source in HCU and aerosol transmission pathway; other water reservoirs contaminated; hypothesis of contamination from water system or at factory; description of four additional patients.
Kohler *et al.* [17▪▪]	Zurich, Switzerland	Description of 10 Swiss, German, and Dutch patients.
Götting *et al.* [10]	Freiburg, Germany	Confirmation of aerosolization, no evidence for water-to-blood leakage through oxygenator in experiment with prolonged simulated extracorporeal circulation.
Haller *et al.* [16▪]	Robert Koch Institute, European Centre for Disease Prevention and Control	Five cases from Germany, positive cultures at LivaNova/Sorin factory.
Tan *et al.* [19]	Rochester, USA	Three cases in USA; two cases with ocular involvement as diagnostic hint.
Garvey *et al.* [11▪]	Birmingham, UK	Biofilm visualization; successful decontamination of HCU including tubing change and two consecutive decontamination cycles.
Sommerstein *et al.* [21▪▪]	Zurich, Switzerland	Evidence for aerosol transmission with smoke video simulation, particle counting, and sedimentation plates; the airstream generated by HCU reaches the ultraclean ventilation system.
Sommerstein *et al.* [30]	Bern, Switzerland	Description of HCU placement outside operating room.
Schreiber *et al.* [31▪▪]	Zurich, Switzerland	Cohort study with five, in 2014 factory-new, LivaNova/Sorin HCUs, monthly surveillance cultures for *M. chimaera* of HCU water and exhaust air; reemergence of *M. chimaera* in HCU water samples after circa six months despite intensified maintenance protocol; air cultures remained without mycobacterial growth.
Perkins *et al.* [27]	USA	11 patients, five HCUs, maximum of 38 SNPs distance with WGS.
Robinson *et al.* [29]	Australia	10/15 HCU positive for *M. chimaera*; in WGS genetic relatedness between isolates of 10 HCUs across four hospitals, but not related to one cardiac surgery-associated case.
Struelens *et al.* [29]	European Centre for Disease Prevention and Control	Editorial to Robinson JO *et al.* and Truzinski FC *et al.* Description of differences between HCU and extra-coporeal membrane oxygenation devices in the context of *M. chimaera* contamination.
Trudzinski *et al.* [13]	Germany	10 ECMOs, nine of 18 samples positive for *M. chimaera* but negative air cultures and negative surface cultures; three patients with bronchial colonization after ECMO support.
Sacco *et al.* IDCases 2017;7:1–3	US Mayo	Case report of 63 year old female; immune thrombocytopenia; thrombocytopenia correlates with disease intensity.
Cai *et al.* Can J Anaesth. 2017;23:513–516	US Mayo	Case of 63 year old female with index surgery in 2010, symptom start in 2015, misdiagnosis as amyloidosis and treated with steroids.
Sommerstein, Schreiber *et al.* Infect Control Hosp Epidemiol 2017;38:103–8.	Switzerland/US	Review summarizing current knowledge and providing preliminary recommendations.
Baker *et al.* [24▪▪]	USA	Outbreak caused by *Mycobacterium abscessus* associated with water system in phase 1 and HCU in phase 2; 22 patients with extrapulmonary invasive disease caused by *M. abscessus*, nine patients died within 60 days; decrease in cardiac surgery-associated *M. abscessus* infections after intensified HCU disinfection and use of sterile water with HCUs strongly suggests that *M. abscessus* is also a problem with HCU technology.
Williamson *et al.* [5]	Melbourne, Australia	Description of a clonal *M. chimaera* lineage from Australia and New Zealand in WGS; 43 samples from Stöckert (now LivaNova) 3T and from five patients; one patient sample identical to two HCU isolates of a center where the patient was re-operated

Table 1 (*Continued*)

Publication	Origin	Contribution to understanding the problem
Chand *et al.* [12▪▪]	UK	Case identification by national laboratory and hospital admissions data linkage: 18 patients in 11 hospitals 2007–2015 (3 months - 5 year latency) of whom nine with fatal outcome, cohort study for risk assessment; WGS patterns show cluster between probable cases and 86% of Sorin (now LivaNova) HCU isolates. HCU investigations: localization of aerosol release through breaches in tanks of Sorin (now LivaNova) 3T HCUs; detection of *M. chimaera* in three of six Maquet HCU 30, four of four Maquet HCU 40, but negative air cultures.
Kanamori *et al.* Clin Infect Dis 2017 Feb 1;64 : 343–6	UK	Editorial to Chand M *et al.* 2017. Delineation of potential advantages and disadavantages of notification of patients exposed to a HCU.
Zweifel [20▪]	Zurich, Switzerland	Case series of five patients from published Zurich case series window to systemic; 'eye as window to systemic infection'.
Hamilton *et al.* Water Research, 2017;1 : 310-26	US	Review addressing the risk of exposure with nontuberculous mycobacteria from water sources in healthcare settings.
Nguyen *et al.* J Thoracic Cardiovasc Surg, in press	US	Discussion of ethical aspects of the *M. chimaera* outbreak on the background of cases at the Mayo clinic.
Stewardson *et al.* Med J Aust 2017;206 : 132–5	Australia	Review highlighting the relevance of the *M. chimaera* outbreak for Australian physicians.
Svensson *et al.* [26▪]	Denmark	18/21 (86%) HCU positive for *M. chimaera*: 14/16 Sorin 3T (now LivaNova) and 4/5 Maquet, but no associated patients in WGS analysis, strain isolated from Maquet HCU was distinct from those from Sorin HCU; Sorin strain nearly identical to isolates from US and UK; description of preventive measures (encasing in one, HCU repositioning in the operating room and more frequent decontamination in two, and placement outside operating room (preexisting) in two centers).
Bursle *et al.* Infection, Disease & Health (2017) 22, 1e5	Australia	Report on first case from Australia, WGS match between patient isolate and HCU

ECMO, extracorporeal membrane oxygenators; HCU, heater–cooler units; SNP, single-nucleotide polymorphisms; WGS, whole genome sequencing;

modifications in the manufacturing process [16▪]. *M. chimaera* was also detected in HCUs from other brands [18]. Additionally, *M. chimaera* was found in extracorporeal membrane oxygenators and water fountains [9▪▪,13].

EPIDEMIOLOGIC AND CLINICAL ASPECTS

M. chimaera invasive disease incidence seems relatively low with 0.17–3 per 1000 procedures at risk [12▪▪]. Data from the United Kingdom from 2007 to 2014 demonstrate an overall incidence of 0.39 cases per 10 000 person years with the highest incidence in 2013 [12▪▪]. Contrasting the wide distribution of LivaNova HCUs, little is known on the true geographical distribution of *M. chimaera* infections. So far, cardiac surgery-associated cases were only reported from Switzerland, the Netherlands, Germany [17▪▪], UK [12▪▪], USA [19], Australia [29], and New Zealand [5].

The spectrum of infections caused by *M. chimaera* includes endocarditis, sternal, vascular graft, and disseminated infections [17▪▪]. Prominent clinical findings can be observed with ophthalmological examination [19,20▪] and the dynamics of retinal involvement might allow monitoring of treatment response. Cardiac surgery-associated *M. chimaera* infections have a poor prognosis and sustained cure remains uncertain. In the largest published case series to date, case fatality rate was around 50% despite treatment with at least three active antibiotics combined in many cases with revision surgery [17▪▪]. *M. chimaera* still grew in tissue samples after several months of targeted antibiotic combination therapy consisting of clarithromycin, rifabutin, ethambutol, and transiently quinolones. Typically, latency up to 5.1 years (median, 21 months) between cardiac surgery and manifest *M. chimaera* infection has been observed [12▪▪]. Frequently reported symptoms include fever,

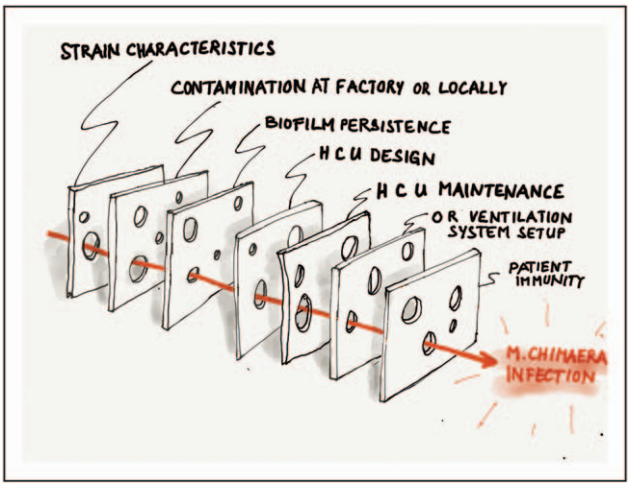

FIGURE 1. Swiss Cheese Model applied to *Mycobacterium chimaera* infections in cardiac surgery. The swiss cheese model was proposed by Dante Orlandella and James T. Reason of the University of Manchester in 1990 to illustrate that multiple failure modes must align to produce an accident. Here we demonstrate a possible explanation why so far only relatively few patients were infected despite the global use of heater–cooler unit technology. HCU, heater–cooler unit; OR, operating room.

weight loss, and shortness of breath [17▪▪]. Lymphopenia, thrombocytopenia, anemia, elevated creatinine, and transaminases as well as C-reactive protein are often encountered [17▪▪]. Misdiagnosis is common. Notoriously, histology of granulomatosis has resulted in misdiagnosis as sarcoidosis, leading to immunosuppressive treatment with unfavorable consequences.

PREVENTING TRANSMISSION

To guarantee protection against contaminated bioaerosols, HCU have been outplaced in an adjacent room [10,30]. Notably, an ajar door may allow bioaerosols to float back into the operating room [10]. The maximum allowed HCU tubing length is a limiting factor to this solution. Purpose-built airtight encasings for LivaNova 3T HCUs directly connected to the ventilation system of the operating room have been successfully produced [31▪▪]. This solution required an individual technical assessment of the overall air flow management to be well tolerated, but if feasible, cost might be inferior to those for architectural solutions.

HEATER–COOLER UNIT DECONTAMINATION AND MAINTENANCE

Studies testing HCU decontamination and maintenance procedures either used solid media [10], mycobacterial growth indicator tubes [29], or both [9▪▪,31▪▪], and various water volumes, reflecting the lack of a standard and limiting comparison.

In a recent report, water samples from a cohort of five factory-new LivaNova 3T HCUs in use for 6 months tested positive for mycobacteria, mostly *M. chimaera* under an intensified maintenance protocol including daily water changes [31▪▪]. All air samples remained negative for *M. chimaera*, probably because of a low bacterial burden. Garvey *et al.* [11▪] published a report on successful decontamination of *M. chimaera* contaminated LivaNova 3T HCUs. The authors used a comprehensive approach with mechanical removal of biofilm, replacement of HCU parts, and two consecutive peracetic acid disinfection cycles. Mycobacterial suppression for a period of 3 months after initial decontamination was achieved under intensified maintenance with daily water changes using filtered tap water and added hydrogen peroxide, and weekly peracetic acid disinfection cycles. Sustainability must yet be established.

DISCUSSION

The outbreak is yet another example of contamination of a complex medical device and other unintended consequences that has required an international investigation and effort. Although the extent of this outbreak is yet unknown, the current global case count is relatively low when compared to other causes of surgical site infections. This rarity can be explained by a stochastic phenomenon or alternatively, by the alignment of several safety breakdowns that are best illustrated by the Swiss Cheese Model (Fig. 1). It must be assumed, however, that many patients remain undiagnosed or misdiagnosed because of insufficient physician knowledge about this disease and likely, a lack of understanding potential risks associated with such complex equipment. Reactivation after years of latency might occur as known with *M. tuberculosis*. Case detection remains challenging because of missing diagnostic tests in latency. Most guidelines recommend targeting patients with prior HCU exposure and unclear inflammatory disease, especially with granulomatous manifestations.

Various HCU brands have proven to harbor *M. chimaera,* nontuberculous mycobacteria and other potential pathogens. Even if cases so far have only been associated with LivaNova 3T, safety of other models and brands has yet to be formally established. Consequently, before proof of well tolerated HCU technology becomes available, the air volume in contact with HCU must be controlled either by encasing the unit or placing it in a separate

room with controlled ventilation, especially if proven contaminated with *M. chimaera*. Relying entirely on negative mycobacterial HCU water and air cultures might be risky until culture test sensitivity is established.

The outbreak brings several lessons to the medical community. First, the delayed outbreak investigation and mitigation highlights a striking mismatch between a global industry distributing sophisticated technology widely from one factory and the fractioned public health authority systems reacting with delay. Second, only an elegant and painstakingly thorough outbreak investigation by several international groups revealed and identified the aspects of this equipment that led to patient harm. Third, airflow producing devices can disrupt the genuine ventilation design and create microbiologic risks. Fourth, being an apparently irreplaceable heat transport medium, water cannot be maintained sterile in HCU and once established, removing biofilm-associated nontuberculous mycobacteria seems uncertain. Fifth, nontuberculous mycobacteria are to be added to the list of pathogens in healthcare water and air safety to pair *Legionella* spp. and *Aspergillus* sps. And finally, complex medical equipment should be thoroughly tested by a third party prior to market introduction, especially in its context of use often constituting a complex system that notoriously produces unexpected risk constellations, and permanently and proactively monitored for unintended consequences.

CONCLUSION

By pure chance and a consequent investigation, an inane patient safety breach was uncovered in the sophisticated and high-stake environment of cardiac surgery. This breach is best described by the Swiss cheese model of aligning failure modes leading to catastrophe (Fig. 1). The extent of the harm done has yet to be seen. Immediate action is warranted both, to identify infected individuals and have them benefit from early treatment, and to prevent further infections by swift action. It would be desirable that forces could be joined across research teams, authorities, and industries globally to rapidly produce a well tolerated alternative for intraoperative temperature management in cardiac surgery.

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Conflicts of interest

There are no conflicts of interest.

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